Update on COVID-19 vaccines & immune response

THE LATEST ON THE COVID-19 GLOBAL SITUATION & VACCINES
Current global situation

CASES REPORTED TO WHO AS OF 7 MARCH 2021, 10:00 CEST

• Cases: > 116 million
• Deaths: > 2.5 million

* Data are incomplete for the current week. Cases depicted by bars; deaths depicted by line.
Immune response to a viral infection

Two types of immunity are:

- **Innate immunity**
  - General immediate response to ANY infection

- **Adaptive immunity**
  - Specific response to an infection
  - Involves the **cellular response** (T cells) and the **antibody response** (B cells)

- Innate immune response is immediate; whereas cellular & antibody response usually starts after 6 to 8 days

*Figure.* Immune response to viral infection
Response in an immunized person

- When adaptive immune cells (B cells and T cells) encounter the same virus again, they respond rapidly and the immune system can effectively clear an infection before it causes disease.
- Vaccines use this immune memory to protect us from infection.
- Immune memory can result from a prior infection or from an effective vaccine.

Figure. Immune response to an immunized person

<table>
<thead>
<tr>
<th>Infection</th>
<th>Virus amount</th>
<th>Cellular response</th>
<th>Antibody response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
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</tbody>
</table>

Strong and rapid antibody response
An immune response is induced by vaccines

- **Vaccines safely deliver an immunogen** (antigen able to elicit an immune response) to the immune system in order to train it to recognize the pathogen when it is encountered naturally by activating:

- **CD4+ helper T cells** that in turn stimulate:
  - **B-cells** to produce neutralizing antibodies specific to the virus
  - **CD8+ cytotoxic T cells** to recognize and kill cells infected by the virus

Kylie Quinn; [https://theconversation.com/could-bcg-a-100-year-old-vaccine-for-tuberculosis-protect-against-coronavirus-138006](https://theconversation.com/could-bcg-a-100-year-old-vaccine-for-tuberculosis-protect-against-coronavirus-138006)
The immune response

- An immunogen is a specific type of antigen that is able to elicit an immune response
- The choice of immunogen for vaccines impacts what type of immune response is induced; as well as safety, development time, production time, costs and access to vaccines
- Immunogens used in current COVID-19 vaccines or COVID-19 vaccines in development:

<table>
<thead>
<tr>
<th>IMMUNOGEN</th>
<th>WHAT IT IS</th>
<th>ADVANTAGE</th>
<th>DISADVANTAGE</th>
<th>EXAMPLE OF VACCINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated virus</td>
<td>Inactivated dead virus</td>
<td>Induces strong antibody response</td>
<td>Requires large quantities of virus, low or no cellular response</td>
<td>Influenza, rabies hepatitis A</td>
</tr>
<tr>
<td>Viral subunit</td>
<td>A protein derived from a pathogen</td>
<td>May have fewer side effects than whole virus (redness, swelling at injection site)</td>
<td>May be poorly immunogenic; complex process</td>
<td>Influenza</td>
</tr>
<tr>
<td>Viral vector</td>
<td>Viral pathogen expressed on a safe virus that doesn’t cause disease</td>
<td>Rapid development, strong cellular response, relatively easy to produce</td>
<td>Prior exposure to vector virus (eg. adenovirus) may reduce immunogenicity, some vectors require boosting with a different vector</td>
<td>Ebola</td>
</tr>
<tr>
<td>Nucleic acid</td>
<td>mRNA coding for a viral protein</td>
<td>Strong cellular immunity; rapid development</td>
<td>Relatively low antibody response</td>
<td>COVID-19</td>
</tr>
</tbody>
</table>

Table. Advantages and disadvantages of immunogens used in vaccines
In inactivated virus vaccines, the genetic material of the virus has been destroyed to stop disease producing capacity.

Inactivated virus cannot replicate inside the body, so higher doses are needed.

Sometimes, an adjuvant (molecules that stimulate the immune system) is used to help strengthen the immune response.

Inactivated virus vaccines generally only induce antibody-mediated immunity (not cell-mediated immunity).

https://www.intvetvaccnet.co.uk/blog/covid-19/vaccine-eight-types-being-tested
Viral subunit vaccines

• Subunit vaccines use the antigen of the virus without any genetic material, usually with an adjuvant to give a better immune response

• Usually made using recombinant expression system (made in a cell without using the virus)

• With the help of antigen-presenting cells, the antigens are recognised by T helper cells as with a real viral infection

• Subunit vaccines generally induce mainly antibody-mediated immunity

• Adjuvants can enhance antibody response and also cell-mediated immunity

https://www.intvetvaccnet.co.uk/blog/covid-19/vaccine-eight-types-being-tested
Viral vector vaccines

- Viral vector vaccines use a non-coronavirus vector modified to include a gene that encodes a target antigen.
- Examples: adenovirus, measles virus, vesicular stomatitis virus.
- Can be replicating or non-replicating.
- Non-replicating: infects a cell and produces SARS-CoV-2 antigen in that cell but not new virus.
- Replicating: upon infection produces SARS-CoV-2 antigen in that cell and new virus which infects other cells.
- The SARS-CoV-2 antigen inside cells seen by body as if SARS-CoV-2 infection and induces T helper cells and cytotoxic T cells.

https://www.intvetvaccnet.co.uk/blog/covid-19/vaccine-eight-types-being-tested
RNA vaccines

- RNA vaccines are antigen-coding strands of **messenger RNA (mRNA)** delivered inside a lipid coat.
- Once inside cells, the mRNA is translated **the protein antigen**.
- The antigen is recognised, inducing an immune reaction.
- Seen by body as if virus inside cell so induces T-helper and cytotoxic T-cells, and antibodies.
- mRNA also recognised by cells as ‘pathogen’ stimulating strong immune response.

https://www.intvetvaccnet.co.uk/blog/covid-19/vaccine-eight-types-being-tested
Preclinical & clinical development of COIVD-19 vaccines

- As of 5 March 2021, there are **79 COVID-19 candidate vaccines in clinical development** of which **12 are in Phase III trials and 4 are in Phase IV**
- There are another 182 candidate vaccines in preclinical development
- More than 90% of all top candidate vaccines will be delivered through **intra-muscular injection**

*Source: 23 February 2021*
*https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines*
Most COVID-19 vaccines are designed for a two-dose schedule

- Two dose vaccination (prime-boost) works by mimicking natural immunity. The first dose primes immunological memory and the second dose solidifies it.

- After a first vaccine dose, the immune system needs time to generate a response and to create memory cells that will recognize the pathogen if it is encountered again.

- A larger time interval between the first and second dose may induce a stronger immune response compared to a short interval*

  - preliminary data from Astra Zeneca’s COVID-19 vaccine trials show that a 12-week prime-boost interval may result in improved vaccine efficacy\(^1,2\)

\*An interval of 21-28 days between the doses is recommended for the mRNA vaccines (Pfizer-BioNTech and Moderna)


Relationship between neutralizing antibody binding 28 days after second dose, and vaccine efficacy against symptomatic COVID-19 of ChAdOx1 nCoV-19\(^1\) (AstraZeneca COVID-19 vaccine)
## COVID-19 vaccine candidates in phase III or phase IV trials

<table>
<thead>
<tr>
<th>16 CANDIDATES - VACCINES IN PHASE III CLINICAL EVALUATION</th>
<th>Vaccine platform</th>
<th>WHO EUL</th>
<th>Already in use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer/BioNTech + Fosun Pharma*</td>
<td>RNA based vaccine</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Moderna + National Institute of Allergy and Infectious Diseases (NIAID)*</td>
<td>RNA based vaccine</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CureVac AG</td>
<td>RNA based vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AstraZeneca + University of Oxford*</td>
<td>Viral vector (Non-replicating)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CanSino Biological Inc./Beijing Institute of Biotechnology</td>
<td>Viral vector (Non-replicating)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamaleya Research Institute ; Health Ministry of the Russian Federation</td>
<td>Viral vector (Non-replicating)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Janssen Pharmaceutical</td>
<td>Viral vector (Non-replicating)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Sinovac Research and Development Co., Ltd</td>
<td>Inactivated virus</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Sinopharm + China National Biotec Group Co + Wuhan Institute of Biological Products</td>
<td>Inactivated virus</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Sinopharm + China National Biotec Group Co + Beijing Institute of Biological Products</td>
<td>Inactivated virus</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Institute of Medical Biology + Chinese Academy of Medical Sciences</td>
<td>Inactivated virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research Institute for Biological Safety Problems, Rep of Kazakhstan</td>
<td>Inactivated virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bharat Biotech International Limited</td>
<td>Inactivated virus</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Novavax</td>
<td>Protein subunit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences</td>
<td>Protein subunit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zydus Cadila</td>
<td>DNA based vaccine</td>
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</tbody>
</table>
COVID-19 vaccine administration

- As of 8 March, more than 349 million vaccine doses have been administered:
- Different vaccines (3 platforms) have been administered (Pfizer, Moderna, Oxford/AZ, Gamaleya, Sinopharm, Sinovac, Bharat Biotech)

Source: Data retrieved from WHO dashboard on 08 March 2021, [https://covid19.who.int/](https://covid19.who.int/)
SARS-CoV-2 variants & COVID-19 vaccines

- Current SARS-CoV-2 variants involve mutations to the gene for the spike protein that is targeted by COVID-19 vaccines.
- Several COVID-19 vaccines have reported reduced efficacy to protect against mild to moderate disease in people infected with SARS-CoV-2 variants, however the vaccines are still expected to protect against severe disease and death.
- Studies are ongoing to examine if some vaccines may be more susceptible to effects of variants than others:
  - those using smaller epitopes (the receptor binding domain on the spike protein) may be more susceptible than those using a larger part of the virus such as the spike protein or the whole inactivated virus.
- Other studies are exploring the development of COVID-19 vaccines that make it difficult for the virus variants to evade immunity, for example:
  - multivalent vaccines that include both new (derived from variants) and old forms of the spike protein in a single dose.
  - vaccines that target multiple sites on several viral proteins in contrast to vaccines that target only the SARS-CoV-2 spike protein.

https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
**Preliminary COVID-19 vaccination results**

- A recent study showed that two doses of the Pfizer BioNTech vaccine prevented 94% of symptomatic COVID-19 cases, 87% of hospitalizations and 92% of severe disease in 596,618 people vaccinated between 20 December and 1st of February in Israel.

- Preliminary results from Scotland, show that four weeks after the first doses of the Pfizer BioNTech and Oxford AstraZeneca vaccines were administered the risk of hospitalization from COVID-19 fell by up to 85% and 94%, respectively. Combined effectiveness for people over 80 was 81%.

### Table. COVID-19 vaccine effectiveness in Israel

<table>
<thead>
<tr>
<th>Vaccine effectiveness</th>
<th>14-20 days post dose 1</th>
<th>≥7 days post dose 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented infections</td>
<td>46% (40-51%)</td>
<td>92% (88-95%)</td>
</tr>
<tr>
<td>Symptomatic COVID-19</td>
<td>57% (50-63%)</td>
<td>94% (87-98%)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>74% (56-86%)</td>
<td>87% (55-100%)</td>
</tr>
<tr>
<td>Severe disease</td>
<td>62% (39-80%)</td>
<td>92% (75-100%)</td>
</tr>
</tbody>
</table>

The allocation of COVID-19 vaccines is guided by public health objectives. For the initial phase these objectives are:

- Reduce mortality
- Protect health systems

To maximise the public health impact of a limited supply of COVID-19 vaccines, the global vaccines allocation mechanism targets:

- **High risk groups** (people over the age of 65, people with cardiovascular diseases, cancer, diabetes, chronic respiratory disease or obese) to reduce severe disease and mortality
- **Health workers** to protect the health system

These groups correspond to 20% of the global population.

Therefore, the first phase of COVID-19 vaccines allocation will be up to 20% of a country’s population.
To keep in mind

Because of the limited supplies, we need to maximize the impact by targeting the high risks groups

WHO recommends prioritization based on the SAGE Prioritization Roadmap
At risk groups to be vaccinated first, such as older adults, persons with underlying conditions, health workforce

In order to:
- to reduce the severe cases among those populations
- to relieve congestion in health care settings
- to leave easy access for the entire population in need of healthcare that is not related to COVID-19
- to reduce mortality

Vaccination is one tool in our toolbox, we will need to use the other tools as well such as Public Health and Social Measures
COVID-19 protective measures
Protect yourself & others

- Keep your distance
- Wash your hands frequently
- Cough & sneeze into your elbow
- Ventilate or open windows
- Wear a mask